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Management for Spinal-Induced Hypotension in Elective Cesarean Section

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ABSTRACT

Title: Management for Spinal-Induced Hypotension in Elective Cesarean Section

Background: Spinal anesthesia (SA) is the preferred method of anesthesia for cesarean section, but is associated with hypotension and bradycardia, which may be deleterious to both parturient and baby. Numerous studies reporting the incidence are as high as 80-100% if without adequate prophylaxis. Currently, several methods have been described to reduce the incidence of spinal anesthesia induced hypotension during cesarean delivery, including left uterine displacement, vascular filling with crystalloid or colloid, use of lower-leg compression and vasopressors, but no single technique has been confirmed to be completely effective. Recent studies suggest that ondansetron also affects hypotension and phenylephrine by infusion is emerging as the vasopressor of choice, titrate to baseline pressure.

Purpose: The purpose of this case study is to utilize current evidence on anesthetic management with maternal hypotension under spinal anesthesia, including administration of ondansetron before spinal anesthesia, optimizing patient preload/co-load with intravenous fluid and vasopressor administration.

Process: An initial literature search with MEDLINE and CINAHL were undertaken (year 1990 to 2016), to find all quantitative studies that parturients of any ethnicity underwent spinal anesthesia for elective cesarean delivery, followed by analysis of the text words contained in the abstract and the index terms used to describe the article. A secondary search using all identified keywords, additional reports were from reference lists of retrieved articles and a total of 32 articles were obtained. Search engines including CINAHL, MEDLINE, Nursing@OVID and Clinical Key were utilized. Only studies published in English and year 2010 onwards were considered unless that study was pertinent in this topic. Only RCT and meta- analysis were considered for the review.

Results: Prophylaxis administration of ondansetron and preload/ co-load method were adopted. The patient in the case report did not encounter maternal hypotension or nausea/vomiting after administration of spinal anesthesia. No prophylactic phenylephrine infusion or other vasopressor boluses were required during the procedure.

Implications: There is no single method that prevents spinal induced hypotension.

Keywords: cesarean section, spinal anesthesia, ondansetron, vasopressor, phenylephrine, ephedrine, prophylaxis, hypotension

Management for Spinal-Induced Hypotension in Elective Cesarean Section

In the United States (U.S.), spinal anesthesia is used for the majority of elective and about half of emergency cesarean deliveries. Spinal anesthesia (SA) has become the gold standard anesthetic technique for elective cesarean section (Trabelsi et al., 2015). It is a simple, fast performed, powerful, and reliable technique that avoids the depressant effects of anesthetic drugs, and allows the mother to be awake during and immediately after delivery (Friedly & Simmons, 2015). In addition, spinal anesthesia is preferable than general anesthesia (GA) as GA is associated with a higher incidence of hemorrhage – the leading cause of maternal death worldwide. Also, GA requires securing the parturient airway by tracheal intubation, which has an increased failure rate that is eight times higher (one in 274) than the general population (Friedly & Simmons, 2015). Both problems lead to an increase in mortality.

Despite the popularity of SA, it is not without side effects. Maternal hypotension is a well-known complication with numerous studies reporting the incidence as high as 80-100% if without adequate prophylaxis (Hessen et al., 2016; Gao et al., 2015), and is associated with other adverse effects such as bradycardia, nausea and vomiting. If severe, maternal hypotension can result in detrimental consequences to the mother such as dyspnea, loss of consciousness, aspiration, and cardiac arrest (Hessen et al., 2016). These complications can significantly impact patient outcomes. Hence, identification of interventions for effective

prevention and/or proactive minimization of hypotension is imperative for improved safety to both parturient and fetus.

Case Report

A 38-year-old, 58.6kg, 1.55m, gravida 3, para 2, 39 weeks' gestation, ASA 2 female, presented for an elective cesarean section with tubal ligation. On admission, vital signs were: blood pressure (BP) 138/70 mm Hg, heart rate (HR) 76 /min, respirations 20/min, temperature of 36.5 ºC with a Body Mass Index was 32.8 kg/m^2. Laboratory values were hemoglobin 11.6 gm/dL, and platelet count of 228,000 µL. Her previous two pregnancies were uncomplicated and deliveries were uneventful. Her surgical history included two previous cesarean sections and a tonsillectomy in childhood. Medical history was unremarkable. Her current medication consisted solely of prenatal vitamins. She had no known drug allergies and no history of anesthetic complications. A preoperative examination, including airway evaluation was performed and her airway was classified as Mallampati II, thyromental distance greater than three fingerbreadth and neck with full range of motion.

An 18-gauge peripheral intravenous catheter was in place and the patient has preloaded with Lactated Ringers (LR) 800ml (10ml/kg) before she was brought to the operating room. For placement of the spinal anesthetic, the patient was assisted to a sitting position and standard monitoring was initiated. Landmarks were identified and the patient was prepped and draped in the normal sterile fashion. An introducer needle was placed between L3 and L4

interspace and then a 25 gauge Whitacre spinal needle was inserted. Upon return of free-flowing CSF and no blood, bupivacaine 0.75% 1.4ml (10.5mg), fentanyl 20 mcg and morphine 0.2mg were injected and positive swirl times two observed during injection. Ondansetron 4 mg IV was given immediately after the spinal anesthetic was administered. The patient was then placed in supine with left uterine displacement and a T4 dermatome level was obtained.

Oxygen was administered via nasal cannula at 3L/min and cefazolin 2 gm IV was given prior to incision for infection prophylaxis. The first vital sign after spinal placement was BP 137/68 mmHg, HR 105/min and NBP were monitored every 2.5 minutes. The SBP were between 135 – 120 mmHg before skin incision and then 134 – 105 mmHg for the whole procedure. The patient had no nauseous feeling and no vasopressors (ephedrine/ phenylephrine) was given. The fetus was delivered 15 minutes after incision. An infusion of oxytocin 20 units in a 1000 ml bag of LR was commenced after delivery. A viable infant weighing 7 pounds 8 ounces with Apgar scores of 8 and 9 at 1 and 5 minutes respectively. The estimated blood loss for the case was 700 ml and 1500 ml of LR was administered intraoperatively.

The patient was transported to the post anesthesia care unit (PACU) on room air. She did not experience PONV nor require additional pain medication in the PACU. A postoperative hemoglobin was 10.4 gm/dL, which was slightly lower than the preoperative hemoglobin. By

postoperative day 3, the patient was doing well; ambulating, voiding, tolerating general diet. Her pain was well controlled with oral pain medications, and was discharged to home.

Methodology

The comprehensive search strategy for the literature review was aimed to find all quantitative studies that include parturients of any ethnicity underwent spinal anesthesia for elective cesarean delivery were considered. An initial search of MEDLINE and CINAHL were undertaken (year 1990 to 2016) followed by analysis of the text words contained in the title and abstract and the index terms used to describe the article. A secondary search using all identified keywords, additional reports were identified from reference lists of retrieved articles and a total of 32 articles were obtained. Only meta-analyses and research studies that were randomized controlled trials were considered for the review.

Keywords and text words with alternate spellings: cesarean section OR cesarean delivery, spinal anesthesia, ondansetron OR 5-HT_3 antagonist, vasopressor OR phenylephrine OR ephedrine, prevention OR prophylaxis, hypotension OR low blood pressure. Search engine including CINAHL, MEDLINE, Nursing@OVID and Clinical Key were utilized. Only studies published in English and year 2010 onwards were considered unless a particular study was pertinent to the topic of maternal hypotension following spinal anesthesia.

Discussion

Spinal anesthesia is produced by the injection of local anesthetic, often together with an opioid adjunct, into the subarachnoid space, with the objective of blocking conduction in afferent sensory fibers that transmit pain impulses to the brain. However, the conduction block from a local anesthetic is non-specific and preganglionic fibers to the sympathetic chain are also affected, resulting in sympathetic block and hypotension which can cause hypoperfusion of the uterus and placenta (Khaw et al., 2006).

Risk Factors

Pregnancy by itself is a risk factor for hypotension under neuraxial block for several reasons: epidural vein engorgement and dural sac compression by the gravid uterus, together with greater sensitivity to local anesthetics gives a higher level of block for a given dose of local anesthetic (Ngan Kee, 2010). Pregnancy also tends to induce a relative increase in sympathetic activity making the effects of blockade more profound (Hobbs & Cockerham, 2013). Other risk factors including preoperative hypertension, age older than 35, pregestational body mass index greater than 25 kg/m^2, low birth gain in pregnancy, peak sensory block height > T4 – T6, oxytocin use, high resting sympathetic tone (resting heart rate > 80-90 beats per minutes or high preoperative anxiety score), high infant birth weight (Hobbs & Cockerham, 2013).

Management of hypotension during regional anesthesia in obstetric has traditionally been based on the results of animal experiments in pregnant ewes that were performed mainly under general anesthesia in the 1960s and 1970s. In particular, these studies showed that large doses of vasopressors caused vasoconstriction in the uteroplacental circulation, which could result in fetal hypoxia (Khaw et al., 2006). This led to an emphasis on non-pharmacological methods of management of hypotension and the establishment of ephedrine as the vasopressor of choice in obstetric patients. However, the results of current clinical research have questioned the traditional teaching and are having a major influence on the way that we manage hypotension during spinal anesthesia in obstetrics.

Early research to prevent or minimized spinal hypotension focused primarily on techniques to increase blood volume and venous return such as fluid loading, positioning to minimize aorto-caval compression, and leg wrapping. However, these techniques have proven largely ineffective (Gao et al., 2015). In recent years, many studies have linked maternal hypotension following spinal anesthesia to Bezold-Jarish reflex (BJR), a form of vaso-vagal syncope triggered by the sympathetic blockade and resulting decreased peripheral vascular resistance (Friedly & Simmos, 2015).

Patient Positioning

The use of left uterine displacement or table tilt to prevent aortocaval compression is a routine in obstetric anesthesia that is supported by history and tradition (Hobbs & Cockerham,

2013). However, Khaw (2006) claimed that there is no clear evidence to support the use of any particular angle of tilt, the optimal degree of tilt is unknown and anesthesiologists often overestimate the amount they apply. Bamber and Dresner (2003) randomly looked into 33 women during the third trimester in seven positions including full lateral, supine and various degrees of right and left table tilt. Apart from the FULL left lateral position in which the patients' cardiac output was significantly higher, they found no benefit whatsoever between the untilted supine position, and the different tilted positions ranging from 2.5 to 12.5 degrees.

Similarly, a randomized study done by Matorras (1998) cited in Khaw (2006) that compared 204 women undergoing emergency cesarean section, of whom 30 received spinal anesthesia found no benefit from a 20-degree table tilt compared with the supine position. There is probably marked individual variability in the susceptibility to aortocaval compression and according to Khaw (2006), it is likely that only a small proportion of women undergoing cesarean section will have aortocaval compression that is severe enough to benefit from lateral table tilt. In the case study, the patient was placed in supine with left uterine displacement with a wedge under right buttock as this is the usual practice of the institution.

Mechanisms of Hypotension During Spinal Anesthesia

The risk of profound hypotension is higher with spinal anesthesia than with epidural

anesthesia, because the onset of the sympathectomy is more rapid and dosing is not titrated. Initially, hypotension is caused by a decrease in systemic vascular resistance (SVR) following pre-ganglionic sympathetic blockade, which leads to peripheral vasodilation and venous pooling (Hessen et al., 2016). Thus, the decrease in blood return to the heart can easily lead to hypotension.

An additional explanation for hypotension in patients undergoing subarachnoid anesthesia is the Bezold-Jarisch reflex (BJR) (Terkawi et al., 2015). This reflex is mediated by serotonin receptors (5-HT_3 sub-type) located on the vagus nerve and within the wall of the cardiac ventricles. They are activated by serotonin released in response to systemic hypotension and cause an increase in efferent vagal signaling. Serotonin induces arterial and venous constriction during hypovolemic states in both humans and animals through an interaction with α-adrenergic receptors and serotoninergic receptors (5-HT_{2A} subtypes). As a result, activation of the BJR causes further inhibition of sympathetic outflow and shifts the cardiac autonomic balance towards parasympathetic dominance, inducing bradycardia while further exacerbating hypotension and vasodilation (Friedly and Simmons, 2015). Research found 5-HT_3 (serotonin) as a potential factor that contributes to induction of the BJR by activating serotonin-sensitive chemoreceptors, especially in the presence of decreased blood volume (Sahoo et al., 2012; Owczuk et al., 2008).

Ondansetron

Mechanism of action. Ondansetron is a selective 5-HT_3- receptor antagonist, blocking serotonin, both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone.

Dose. For prevention of postoperative nausea and vomiting, a single dose is 0.1 mg/kg (≤ 40 kg) and 4 mg (≥ 40kg) given approximately 30 minutes before the end of anesthesia. No dosage adjustment is required for patients that are elderly and/or have renal impairment. The maximum daily dose for hepatic impairment is 8mg (Baughman, Golembiewski, Gonzales, & Alvarez, 2011).

Side effects. There are several known side effects with ondansetron. The most common, those > 10% reported in adult patients, include headache (9 to 27%), malaise/ fatigue (9 to 13%), and constipation (6 to 11%). The specific treatment for ondansetron overdose has not been reported (Wang et al., 2014).

Cost. The hospital purchase cost of ondansetron 4 mg IV for an institution within North Dakota is US $0.29 (K. Kern, personal communication, 2017).

Use of 5-HT3 Antagonist in Bezold- Jarisch Reflex Induced Hypotension

Friedly and Simmons (2015) stated that ondansetron is a highly effective and specific 5-HT_3 receptor antagonist. Therefore, it is strongly believed that ondansetron preloading before spinal anesthesia may prevent hypotension by blocking 5-HT- triggered BJR, suppressing

further expansion of peripheral vessels and increasing blood return to the heart.

Routinely, ondansetron is used for treatment of postoperative nausea, vomiting and intraoperative chills. It was also found effective in preventing hypotension after spinal anesthesia (Wang et al., 2014). Few studies have been conducted to evaluate the effects of 5-HT_3 antagonist on BJR induced hypotension. Sahoo and colleagues (2012) conducted a double-blind randomized, placebo-controlled study on 56 obstetric patients who were ASA physical status I, between 20 and 40 years of age undergoing a lower segment cesarean section with spinal anesthesia. Patients were randomly allocated into two groups receive either intravenous ondansetron 4mg or normal saline 5 minutes before spinal anesthesia. Heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) and oxygen saturation (SpO2) were recorded at the time of spinal drug administration and at 2 minutes' intervals up to 20 minutes, followed by 5 minutes' intervals until the end of surgery. SBP <90 mmHg or DBP < 60 mmHg was treated with IV phenylephrine 50 µg; HR < 50 beats/min was treated with IV atropine 0.3mg. Nausea and vomiting were treated with IV promethazine 12.5mg. Their result indicated that ondansetron prevented the serotonin-induced BJR, suppressed venodilatation, augmented venous return to the heart and result in lesser reduction in SBP and MAP (Sahoo et al., 2012).

Similarly, the clinical presentation of this case study is consistent with Sahoo's study. In this case, the time of ondansetron administration had been discussed with the CRNA.

Eventually, ondansetron 4 mg was given right after the parturient was brought into the operating room and then placed in the sitting position for spinal anesthesia. Both SBP and DBP from spinal injection towards delivery of fetus were within 20% of patient's baseline. The parturient had no complaints of nausea and no vasopressors was given throughout the procedure. Thus, it is possible that the reduction in SBP and MAP were secondary to the administration of IV ondansetron before spinal anesthesia. This would be consistent with one of the results noted in Sahoo's 2012 study. Given that few studies have been done in this area, more research needs to be done in the future to determine if this is a valid relationship that is generalizable.

Optimal Time and Dosage for Ondansetron Injection

Ondansetron has been studied previously for use in spinal anesthesia (Owczuk et al., 2008; Sahoo et al., 2012; Wang et al., 2014; Trabelsi et al., 2015; Khouly, 2016). These studies all concluded that ondansetron 4mg given intravenously 5 minutes before a subarachnoid block reduced maternal hypotension and the occurrence of nausea and vomiting, as well as vasopressor required in parturient women undergoing elective cesarean deliveries. In addition, the results indicated that ondansetron prevent the serotonin-induced BJR, suppressed venodilatation, augmented venous return to the heart and resulted in lesser reductions in SBP and MAP.

Likewise, meta-analyses done by Gao et al. (2015) and Hessen et al., (2016) have

similar conclusions. Gao and colleagues (2015) analysis ten randomized controlled trial with 863 patients with the effects of prophylactic ondansetron on spinal anesthesia- induced hypotension. In eight of ten studies, ondansetron was administrated 5 minutes before spinal anesthesia. They found the relative risk (RR) of hypotension after ondansetron in the obstetric subgroup was 0.16 (95% CI 0.05 to 0.51, P= 0.002). The RR of bradycardia after prophylactic ondansetron was 0.27 (95% CI 0.16 to 0.47, $P < 0.0001$), indicating that prophylactic ondansetron significantly reduced the incidence of bradycardia caused by spinal anesthesia. In addition, they found the mean difference (MD) of ephedrine consumption after prophylactic ondansetron administration was -2.35mg (95% CI -4.14 to – 0.55 mg, $P < 0.05$), suggesting that prophylactic ondansetron significantly reduced the required dose of ephedrine.

Similarly, Heesen et al. (2016) reviewed and analyzed seventeen (8 obstetric, 9 non-obstetric) RCT trials on 2604 patients. The aim of the review was to determine whether 5-HT_3 receptor antagonists administered before the initiation of spinal anesthesia mitigate hypotension. They concluded that 5-HT_3 antagonists are effective in reducing the incidence of hypotension and bradycardia; the effects are moderate and are only significant in the patients undergoing cesarean delivery. Though the effects in the non-obstetric population are not significant.

Although conventional practice and previous studies have shown that ondansetron 4mg preloading can significantly reduce maternal hypotension and nausea, the dose-dependent effect of ondansetron has not been investigated (Wang et al., 2014). Therefore, Wang and colleagues (2014) designed a double-blinded randomized study to compare the efficacy of different doses of ondansetron preloading combined with rapid crystalloid coloading on reducing maternal hypotension during cesarean delivery, they also assessed the effects of different doses on maternal nausea, umbilical venous pH, partial pressure of carbon dioxide (Pco_2), bicarbonate (Hco_3) and base excess in extracellular fluid and neonatal outcome after delivery.

A total of 150 participants were randomly assigned to one of five groups according to computer-generated codes, 30 women in each group. Five minutes prior to spinal anesthesia, the participants in the five groups were intravenously injected with 5ml of physiological saline (S) or 2mg (02), 4mg (04), 6mg (06) or 8mg (08) of ondansetron. If hypotension occurred (defined as systolic blood pressure less than 80% of baseline), an IV bolus of pnenylephrine100 µg was given in the study period (30 minutes). The results revealed that the incidence of maternal hypotension was significantly reduced in groups 04 and 06 ($p< 0.05$) and no bradycardia or vomiting was observed in groups 04, 06 and 08.

Moreover, the consumption of phenylephrine in group 04 was significantly less than that in group S (Wang et al., 2014). Regarding neonatal outcome, the gas analysis results from

umbilical arterial blood showed that there was no significant difference in pH, Pco_2, PO_2, Hco_3or base excess ($P > 0.05$). The pH of the umbilical venous blood was significantly higher in group 04 compared with group S.

Concerning the maternal hemodynamic parameters, the maximum decline of SBP, DBP and MAP was significantly lower in group 04, while minimal changes of mean of SBP, DBP, MAP and HR were observed in group 04 and 06. Wang's (2014) study demonstrated that IV injection of 4 or 6 mg of ondansetron paired with preloading of a rapid crystalloid infusion could significantly reduce the incidence of maternal hypotension and nausea, decrease the Pco2 in umbilical venous blood, and stabilize the maternal hemodynamics. However, lower (2mg) and higher (8mg) doses of ondansetron preloading failed to reduce the incidence of maternal hypotension and nausea. Additionally, 6mg and 8mg of ondansetron might cause light lactate acidosis in the fetus according to the reduced BE value. Therefore, considering its effects on hypotension, nausea, phenylephrine consumption and neonatal outcomes, 4 mg of ondansetron preloading was the optimal dose to prevent maternal hypotension, nausea and other adverse effects during cesarean delivery per Wang's (2014) result.

Intravenous Fluid Therapy – Preload versus Co-load

The American Society of Anesthesiologists Practice Guidelines for Obstetric Anesthesia (2007) state that fluid preloading may reduce the frequency of maternal

hypotension. Traditionally, crystalloid intravenous fluids were administered before the induction of spinal anesthesia for cesarean delivery (preload). The rationale for preload is to maintain or augment cardiac preload and cardiac output (CO) and thus prevent or attenuate hypotension. If the requirement for vasopressor drugs can be reduced, the risk of consequent uteroplacental vasoconstriction may be decreased. Common practice is to infuse approximately 1-2 liters or 10 – 20 ml/kg of lactated Ringer's (LR) solutions while the patient is being prepared for regional anesthesia. Early studies describing fluid preloading had impressive result and became established as an accepted standard of care (Khaw et al., 2006). However, its use has now been largely abandoned due to its relative lack of efficacy in reducing spinal-induced hypotension, even when used in large volumes (Tawfik et al., 2014).

More current evidence has shown that preloading may be unsuccessful in reducing the incidence of hypotension for a number of reasons. Khaw et al. (2006) claimed that the poor efficacy probably reflects rapid redistribution and short clinical half-life (20 to 30 minutes) of crystalloid – only 28% of crystalloid remains in the intravascular compartment when given over 30 minutes. Banerjee et al. (2010) explained that early fluid loading is not effectively increase the intravascular volume at the time of maximum vasodilation. A rapid infusion of LR solution increases the intravascular volume by about 10%, but it decreases rapidly when the infusion is discontinued. On the other hand, preloading may induce atrial stretching, releasing atrial natriuretic peptide. Since natriuretic peptide type C is a potent vasodilator

produced in the endothelium of great vessels, rapid fluid administration (whether before or during induction of anesthesia) may actually exacerbate peripheral vasodilation and facilitate fluid excretion.

In the meta-analysis review by Banerjee and colleagues (2010), the authors aimed to determine whether the timing of the fluid infusion, before (preload) or during (co-load) induction of spinal anesthesia for cesarean delivery influences the incidence of maternal hypotension or neonatal outcome. They were unable to conclude the time of fluid loading, either before or during induction of spinal anesthesia, affected the incidence of hypotension or other side effects in patients undergoing elective cesarean delivery. None of their reviewed studies, that involved total 518 patients, showed a statistically significant difference in the incidence of hypotension between groups. They concluded that the timing of fluid loading does NOT have an impact on the incidence of hypotension and that is true for both colloid and crystalloid loading.

In contrast, a study by Williamson et al. (2009) hypothesized that administering half of the fluid bolus (10ml/kg) before and half immediately following injection of the SAB would provide benefit in reduction of spinal-induced hypotension in parturient. In the RCT study, 87 ASA I or II subjects were investigated. 43 preload (control) and 44 preload/coload (experimental). Subjects assigned to the control group received a 20ml/kg fluid bolus of LR during approximately 20 minutes in the preoperative holding area. This bolus was timed to be

completed just before transport to the operative suite. Once the fluid bolus was given, the infusion rate was decreased to a maintenance rate of 100ml/hr. The experimental group received a 10ml/kg LR preload beginning approximately 10 minutes before transport to the operative suite, and then received a maintenance infusion of 100ml/hr during placement of the SAB. Immediately following injection of the SAB, all subjects in the experimental group were administered an IV bolus of 10ml/kg of LR during approximately 10 minutes and then received a maintenance infusion of 100ml/hr until the conclusion of the cesarean delivery. Hypotension in the study was defined as an SBP of less than 100mmHg or a decrease in mean arterial pressure (MAP) of 20% from the baseline.

The results indicated that, compared with control group, the total volume of LR infused was significantly less ($P = 0.02$) in the experimental group. Analysis of vasopressor use revealed that 31 (72%) of 43 subjects in the control group required ephedrine for blood pressure support compared with 24 (55%) of 44 subjects in the experimental group ($P = 0.09$). The amount of ephedrine and phenylephrine used was higher in the control group than in the experimental group, but this finding did not achieve statistical significance ($P > 0.05$). The authors recommended replacing standardized prophylactic crystalloid fluid administration (20ml/kg preload) with preload/co-load method as described.

In the case report, the parturient was given intravenous fluid in this manner (preload/co-load). She was infused with LR 800ml 10 minutes before brought into the

operating room and 800ml (10ml/kg) co-load right after the spinal injection, then 100ml per hours afterward towards the end of surgery.

Colloid versus Crystalloid

In contrast to crystalloids, colloid solutions have a longer intravascular half-life and are more effective than crystalloids in reducing the incidence as well as the severity of hypotension (Morgan et al., 2001). Recent studies have described the use of albumin, gelatins and hetastarch solutions, some in combination with crystalloids. Using 15ml/ kg of 5% albumin, hypotension was prevented and better condition of the baby was reported and when 500ml of 6% hetastarch was used to supplement crystalloid preload, the incidence of hypotension was halved from 85% to 45% (Khaw et al., 2006).

In a randomized double-blind study by Tawfik et al. (2014), 210 patients were randomly allocated to received either 6% hydroxyethyl starch 500ml before spinal anesthesia (colloid preload) or Ringer's acetate solution 1000ml administered rapidly starting with intrathecal injection (crystalloid co-load). They concluded the use of 1000ml crystalloid co-load has similar effect to 500ml colloid preload and neither technique can totally prevent hypotension and should be combined with vasopressor use. Moreover, colloid is expensive and have potential risks of allergic reactions, disease transmission, and fluid overload, which limits general acceptance in routine clinical practice.

The anesthesia professional should be vigilant in fluid boluses and total fluid infused

due to the physiologic changes associated with pregnancy, which places parturient patients are at an increased risk for the development of pulmonary edema. The risk is increased in the setting of large fluid boluses that are often required during spinal anesthesia (Williamson, 2009).

Vasopressors – Ephedrine versus Phenylephrine

In choosing an appropriate vasopressor in obstetrics, several factors need to be considered. These include efficacy, maternal effects other than increasing blood pressure, ease of use, direct and indirect fetal effects, cost, and availability (Ngan Kee & Khaw, 2006).

Vasopressors drugs increase BP by increasing SVR (by vasoconstriction) and/or by increasing CO (by increasing contractility and HR). Postsynaptic α1-receptors in peripheral vessels mediate vasoconstriction and stimulation of postsynaptic β1-receptors in the heart increases HR and cardiac contractility.

Ephedrine. Ephedrine is a mixed α and β receptor agonist. Its mechanism is both direct (binds and stimulates receptors) and indirect (causes release of norepinephrine from presynaptic vesicles). Ephedrine causes an increase in cardiac contractility, HR, CO and systolic and diastolic BP (Lee et al., 2002). It has a slow onset of action and limited efficacy in prevention and treatment of hypotension. According to Kluger (2000), large doses may be required which increases the chances of unwanted effects. Acute tolerance to ephedrine develops and phenylephrine may need to be added when ephedrine is ineffective or when a

large dose has been given. When large doses of ephedrine are used to restore BP, sustained increases above baseline may occur (Lee et al., 2002). In particular, an important concern about ephedrine in obstetric has been the association between its use and a dose-related depression of fetal pH and base excess.

Although a decrease in uteroplacental blood flow is a possible explanation, the data from animal studies suggest that this is unlikely. An alternative explanation, according to Cooper (2012), is a direct stimulating effect on fetal metabolism. Ephedrine has metabolic stimulatory effects that has led to its use for weight loss and athletic performance enhancement in adults. Metabolic stimulation is particularly noted in brown adipocytes and is thought to be medicated by stimulation of β-adrenoreceptors. Ephedrine crosses the placenta and increase fetal catecholamine concentrations.

Ngan Kee and Khaw (2006) stated that an increase in umbilical arterial norepinephrine concentrations was shown to correlate with decreasing pH. Maternally administered ephedrine increases fetal heart rate and fetal tachycardia can often be observed on the cardiotocograph when large doses of ephedrine are given before delivery in clinical practice.

Phenylephrine. Phenylephrine is chemically related to adrenaline but pharmacodynamically similar to norepinephrine. It is a potent, rapidly-acting vasopressor with a short duration of action that selectively stimulates α-1 adrenoreceptors with very little activity on the β-1 adrenoreceptors of the heart. It increases systolic and diastolic BP in a

dose-dependent manner based purely on its α-1 adrenoreceptor action (Khaw et al., 2006).

Despite different methods described above in preventing and treating hypotension in obstetric anesthesia including IV fluid preload/ co-load and prophylactic preload with 5-HT_3 antagonist, vasopressor is often required. Two commonly used and investigated vasopressors by anesthesia providers are ephedrine and phenylephrine. In fact, there is growing evidence that the choice of vasopressor for treatment of maternal hypotension from spinal anesthesia is controversial (Khaw et al., 2006). The main issues surround efficacy and hemodynamic effects as well as the potential for adverse effects on uteroplacental blood flow and fetal acid-base status as discuss above.

Historically, ephedrine was recommended based on observations in pregnant sheep that showed it was more effective for increasing arterial pressure with better preservation of uteroplacental blood flow compared with other vasopressors. This was explained by ephedrine's predominant β-effect that caused an increase in arterial pressure by increasing cardiac output rather than by vasoconstriction. As such, the use of pure α-agonist such as phenylephrine has generally been avoided because of concerns about their potential adverse effect on uterine blood flow (Lee, 2002).

However, extrapolation from animal studies to humans may not be always appropriate because there are species differences and differences in dose, titration and duration of the administration, and use of IV prehydration to consider (Lee, 2002). In fact, in the systematic

review by Lee (2002), there was no clear evidence that phenylephrine was associated with decreased uterine blood flow because there were few RCTs examining this issue.

In addition, her finding is actually indirect evidence that uterine blood flow may be better with phenylephrine compared with ephedrine. It can be explained that relatively large total doses of ephedrine were required to maintain maternal arterial pressure and the fact that ephedrine exhibits marked tachyphylaxis because its sympathomimetic effects are largely indirect, arising from the release of noradrenaline form postganglionic sympathetic nerve endings that may become depleted after repeated dosing of action and long duration of action. These factors mean that ephedrine may be more difficult to titrate, especially compared with direct-acting vasopressors, which may contribute to suboptimal control of arterial pressure (Lee, 2002).

Subsequently, Ngan Kee and Lee (2008) investigating different factors that may predict uterine arterial pH and base excess, and the authors concluded that in order to minimize the risk of fetal acidosis, ephedrine should NOT be used before delivery and that α-agonist should be the choice for minimizing spinal hypotension. Heesen and colleagues (2015) concurred that there is no advantage to routinely using ephedrine in combination with phenylephrine because it increases maternal nausea compared with phenylephrine alone, phenylephrine has become firmly established as the vasopressor of choice, for both prophylaxis and treatment of spinal hypotension in obstetrics.

Vasopressor Infusion

Currently, research continues to focus on optimizing the administration of phenylephrine. Areas studied have included: how phenylephrine could best be administered; whether it should be used proactively (prophylactically) or reactively (only when spinal hypotension has occurred); whether continuous infusions are superior to bolus administration and the appropriate dose or doses required to avoid unwanted side effects such as reactive hypertension and bradycardia (Hessen, 2015).

A meta-analysis looking at the use of phenylephrine for cesarean section under spinal anesthesia by Hessen (2014) concluded that a continuous infusion (proactive treatment) started *immediately* after initiation of spinal anesthesia can effectively reduce hypotension and nausea without inducing fetal acidosis compared with bolus doses given only in response to a fall in SBP (reactive treatment). It needs to be given immediately following induction of spinal anesthesia because of the rapid decrease in systemic vascular resistance. Prophylactic phenylephrine bolus administration should be followed by an infusion or repeated bolus because of its short duration of action (Cooper, 2012).

Although some anesthesia professionals regard prophylactic administration of phenylephrine as too aggressive, the review by Hessen (2014) revealed that the risk of reactive hypertension did not differ between prophylactic and reactive regimens and the risk of bradycardia was also similar between groups.

In order to develop the reliably and safely infusion regimen that will control the maternal blood pressure, with minimal maternal side-effects while avoiding maternal hypertension, Ngan Kee and colleagues (2005) conducted their studies in phenylephrine infusion regimen. An infusion of phenylephrine 100 μg/min was started immediately after completion of the intrathecal injection and was continued for the first 2 minutes unless SBP exceeded 120% of baseline, in which case it was stopped. After this, the infusion was continued if SBP was less than or equal to baseline, and stopped once it went above baseline. Patient were randomly assigned to two groups depending on the crystalloid infusion received, either a rapid infusion (co-load) group or a minimal maintenance group and they found that total phenylephrine consumption was lower in the group receiving co-hydration.

Other authors have studied different infusion regimens of phenylephrine ranging from 25 to 100 μg/min. Studies by Stewart et al. (2010) and Heesen (2015) both suggested that compared with higher doses, 25 – 50 μg/min offers the most favorable risk/ benefits profile, that is, the lowest rate of both hypotension and hypertension.

In this case study, no phenylephrine infusion has been infused whatsoever as it was not the usual practice of the institution. Phenylephrine and ephedrine syringe bolus were ready to go but eventually SBP and MAP were maintained and no complained of nausea or emesis, thus no vasopressor was given in this case.

The Future Practice – How About Norepinephrine?

Recently, norepinephrine has emerged as a potential alternative agent for the treatment of spinal-induced hypotension in obstetric anesthesia (O'Sullivan & Cockerham, 2016). The reason is the mixed α and β agonist activity of norepinephrine may make it preferable drug for maintaining blood pressure with less bradycardia and no difference in fetal outcome.

In the previous discussion, it was noted that, as compared with ephedrine, phenylephrine is associated with less neonatal acidosis while maintaining uteroplacental blood flow. However, it has also been shown that phenylephrine can have clinically significant side effects such as baroreceptor medicated bradycardia with a consequent decrease in cardiac output (Vallejo et al., 2016). Norepinephrine has weak β- adrenergic receptor agonist activity and therefore may be a more suitable option for maintaining maternal blood pressure with less negative effects on HR and CO compared with phenylephrine. According to Ngan Kee (2015), although treatment of hypotension during spinal anesthesia is listed by the manufacturer as an indication for the use of norepinephrine, there is limited information available for its use for this purpose in the literature and few reports of its used in obstetric patients.

In the recent double-blinded, randomized controlled study by Ngan Kee (2015), 104 healthy patients having cesarean delivery under spinal anesthesia were randomized to have SBP maintained with a computer-controlled infusion of norepinephrine 5 μg/ml or

phenylephrine 100 µg/ml. The primary outcome compared was cardiac output, blood pressure, heart rate and neonatal outcome were also compared. The authors found that an infusion of norepinephrine maintained blood pressure as effectively as phenylephrine, but with less bradycardia and less decrease in cardiac output. Also, no significant differences in neonatal outcomes were found. In this study, utilizing minimally invasive cardiac output monitors have demonstrated marked reduction in systemic vascular resistance and a modest increase in cardiac output, heart rate and stroke volume after induction of spinal anesthesia. This physiological observation is consistent with the findings that α-agonist vasopressors are the most reliable method for preventing and treating spinal hypotension during cesarean delivery.

Another randomized controlled clinical trial by Vallejo et al. (2016) hypothesized that norepinephrine would be superior to phenylephrine, and requiring fewer rescue bolus interventions to maintain blood pressure. Eighty-five parturients having spinal anesthesia for elective cesarean delivery were randomized to Group P (phenylephrine 0.1 µg/kg/min) or Group N (norepinephrine 0.05 µg/kg/min) *fixed-rate* infusion. Rescue bolus interventions of phenylephrine 100 µg for hypotension, or ephedrine 5mg for bradycardia with hypotension, were given as required to maintain SBP. The results confirmed the authors' clinical impression that a fixed rate infusion of norepinephrine is effective for maintaining maternal blood pressure in elective cesarean delivery under spinal anesthesia. When a norepinephrine infusion was used, the number of required rescue boluses of ephedrine was decrease and

fewer patients had emesis compared with a phenylephrine infusion.

Despite the encouraging results from Ngan Kee (2015), Vallejo et al. (2016) and more work is coming out, it is quite certain that it would be unlikely another paradigm shift in vasopressor choice for cesarean delivery. Carvalho (2015) claimed that although there is strong evidence that phenylephrine is a superior agent to ephedrine (e.g. faster onset of action, better fetal acid-base profile, less placental drug transfer, and more effective at increasing systemic vascular resistance), it took many years for clinicians to change practice and for phenylephrine to be considered the drug of choice in this setting.

In contrast, norepinephrine is generally use in the intensive care and cardiac anesthesia setting. Given this lack of familiarity, the shift toward using norepinephrine in the obstetric domain will be challenging. Anesthesia professionals will likely require much convincing with additional research in this area before they are ready for another vasopressor paradigm shift in the management of spinal hypotension during cesarean delivery.

Evidence Based Recommendations

Clinical Recommendations – Preload/ Co-load plus 5- HT_3 Antagonist

In summary, there is no single method that prevents spinal induced hypotension and the management continues to be controversial. In this paper, current management on healthy parturient had been reviewed and the changing trend has been discussed. Prophylactic 5-HT_3 antagonist had a significant effect on the incidence of hypotension in healthy parturient, most

of the studies result support to administer intravenous ondansetron 4 mg five minutes before spinal anesthesia. Crystalloid pre-hydration seems to be of little use and the current focus is on the timing of administration of fluid – preload 10ml/kg (20 minutes before procedure) together with coload 10ml/kg (given in 10 minutes after SAB) instead of preload 20ml/hr - this is based on the half-life of crystalloid stay intravascularly. Though, it is unnecessary to delay surgery in order to deliver a preload of fluid. Regardless of the fluid loading strategy, the incidence of maternal hypotension is high.

Clinical Recommendations – Vasopressor

Prophylactic or therapeutic vasopressors likely to be required in a significant proportion of patients. Base on the review of plentiful meta-analysis on cesarean delivery vasopressor management, the current best-practice recommendation is for phenylephrine infusion starting at 50 mcg/min right after spinal injection and then titrate to response, with bolus if needed. Most experts and academic units have moved away from the use of ephedrine because of its poor efficacy, greater placental transfer and association with fetal acidosis. Thus, it may be prudent to avoid ephedrine before the baby is delivered. But it can be useful when given after delivery because of its longer duration of action.

Future Research

More RCT's work should be conducted to determine the safety of norepinephrine in obstetric patients and investigate whether its use may be associated with greater

uteroplacental blood flow compared with phenylephrine, particularly in conditions where uteroplacental perfusion is restricted such as preeclampsia. Lastly, it is imperative to determine the optimal infusion rate and dosing strategy of norepinephrine for maintaining maternal hemodynamics under spinal anesthesia for cesarean delivery.

Conclusion

Based on the clinical presentation of this case study and review of the latest evidence, a combination of pharmacological and non-pharmacological methods is beneficial in minimizing maternal hypotension following spinal anesthesia in cesarean delivery. Several methods have been described including left uterine displacement, vascular filling with crystalloid preload/ co-load, use of lower-leg compression, vasopressors (bolus versus infusion), as well as intravenous ondansetron 4mg given five minutes before spinal anesthesia may reduce hypotension, phenylephrine requirements and nausea. However, no single technique has been confirmed to be completely effective.

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Appendix A: North Dakota Association of Nurse Anesthetists Meeting Presentation

Management for Spinal-Induced Hypotension in Elective Cesarean Section

Louise Sin, SRNA

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Introduction

- In US, spinal anesthesia is used for the majority of elective cesarean deliveries
- Maternal hypotension is a well-known complication with numerous studies reporting the incidence as high as 80% if without adequate prophylaxis
- Associated with other adverse effects such as bradycardia, nausea and vomiting
- Currently, several methods have been described to reduce the incidence Including:
  - left uterine displacement (LUD), vascular filling with crystalloid or colloid, use of lower-leg compression and vasopressors, but no single technique has been confirmed to be completely effective

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Case Information

- 38 year-old
- 58kg
- Gravida 3, Para 2
- 39 week gestation
- ASA 2
- Presented for an elective c- section with tubal ligation

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Pre-operative Evaluation

- Pre-op VS: BP 138/70, P 76/min
  RR 20/min, Temp 36.5
- Labs: Hgb 11.6 gm/dL, platelet 228
- Past Medical History unremarkable
- NKDA
- Surgical History: two previous c - sections and a tonsillectomy in childhood
- Current medication: prenatal vitamins
- Airway evaluation: Mallampati II, neck FROM

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Anesthetic Course – Spinal Anesthesia

- Pre-load: LR 800ml (10ml/kg) before brought to the OR given within 20 minutes
- Ondansetron 4 mg IV – given before placement of spinal
- Drugs: bupivacaine 0.75% - dextrose 8.25% 1.4ml (10.5mg), fentanyl 20 mcg and morphine 0.2mg
- Placed in supine with left uterine displacement
- T4 dermatome level was obtained
- 3L Oxygen
- Cefazolin 2g IV was given
- Co-load: 800ml (10ml/kg) after spinal block
- Decrease to maintenance rate afterward

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Intraoperative Issues

- The first vital sign after spinal – BP 137/68mmHg, HR 105/min
- NBP was monitored every 2.5 minutes
- The SBP were between 120 -135 mmHg before skin incision and then 105– 134 mmHg for the whole procedure
- Patient had no nauseous feeling and no vasopressors (ephedrine/ phenylephrine) was given
- Baby was born 15 minutes after incision with Apgar score 8 and 9
- EBL was 700 ml with 1.5 liters of LR given intraoperatively

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PACU

- Transported to the post anesthesia care unit (PACU) on room air
- Did not experience PONV nor require additional pain medication in the PACU
- Discharged home on post op day 3

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Discussion

- Traditionally, management of hypotension following regional anesthesia in obstetric has been based on the results of animal experiments in pregnant sheep in the 1960s
- In particular, those studies showed that large doses of vasopressors could result in fetal hypoxia (Khaw et al., 2006)
- This led to an emphasis on non-pharmacological methods and established ephedrine as the vasopressor of choice in obstetric
- However, the results of recent clinical research has declined the superiority of ephedrine and phenylephrine has replaced the choice in current practice (Gao et al., 2015)

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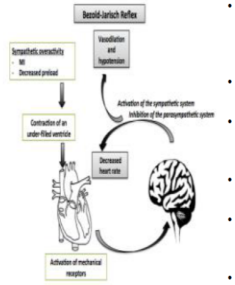
Mechanisms of Hypotension During Spinal Anesthesia



http://www.wikidoc.org/index.php/Bezold-Jarisch_reflex_pathophysiology

- Initially caused by a decrease in systemic vascular resistance (SVR) following pre-ganglionic sympathetic blockade, then leads to peripheral vasodilation and venous pooling
- An additional explanation for hypotension is the **Bezold-Jarisch reflex (BJR)**
- BJR originates from inhibitory mechanoreceptors located in the left ventricle
- The contraction of the poorly filled ventricle stimulate those receptors
- These receptors in turn stimulate parasympathetic pathways and inhibits the sympathetic pathways
- The result of this reflex is a constellation of bradycardia, vasodilation and hypotension

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Use of 5-HT3 Antagonist in Bezold-Jarisch Reflex Induced Hypotension

- Routinely, ondansetron is used for treatment of postop nausea, vomiting, and chills
- Research found 5-HT3 can induce the BJR (Sahoo et al., 2012; Owczuk et al., 2008)
- Sahoo and colleagues (2012) – conducted a double-blind randomized study on 56 ASA I obstetric patients undergoing elective C- section
- Patients were randomly assigned into two groups receive either IV ondansetron 4mg or normal saline 5 minutes before spinal
- Heart rate (HR), systolic (SBP), diastolic (DBP), mean pressure (MAP) and oxygen saturation (SpO2) were recorded
- Their result indicated that ondansetron prevented BJR, suppressed venodilatation, augmented venous return to the heart and result in lesser reduction in SBP and MAP

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Optimal Dosage for Ondansetron Injection

- Wang and colleagues (2014) – designed a double-blinded randomized study to compare the efficacy of different doses of ondansetron on reducing maternal hypotension
- A total of 150 participants were assigned to one of five groups
- 5 minutes prior to spinal, they were injected with 5ml of saline (S) or 2mg (02), 4mg (04), 6mg (06) or 8mg (08) of ondansetron
- The results revealed that the incidence of maternal hypotension was significantly reduced in groups 04 and 06 ($p < 0.05$) and no bradycardia or vomiting in groups 04, 06 and 08
- Regarding neonatal outcome, there was no significant difference in pH, Pco2, PO2, Hco3 or base excess ($P > 0.05$)
- Therefore, considering its effects on hypotension, nausea, phenylephrine consumption and neonatal outcomes, ondansetron 4mg was the optimal dose

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Vasopressor Use in Obstetric

Ephedrine

- Mixed α and β receptor agonist
- Mechanism – both direct (binds and stimulates receptors) and indirect (causes release of norepinephrine from presynaptic vesicles)
- Causes an increase in cardiac contractility, HR, CO, systolic and diastolic BP
- An important concern about ephedrine is the association between its use and fetal acidosis
- Ephedrine has metabolic stimulatory effects that has use for weight loss and athletic performance enhancement in adults
- Maternally administered ephedrine increases fetal HR when large doses of Ephedrine are given before delivery (Ngan Kee and Khaw, 2006)

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Vasopressor Use in Obstetric

Phenylephrine

- Chemically related to adrenaline but pharmacodynamically similar to norepinephrine
- It is a potent, fast-acting with a short duration of action that selectively stimulates α-1 adrenoreceptors with very little activity on the β-1 receptors

- Ngan Kee and Lee (2008) – investigating different factors that predict uterine arterial pH and base excess, and concluded that in order to minimize the risk of fetal acidosis, **ephedrine should NOT be used before delivery** and α-agonist should be the choice for treating spinal hypotension
- Phenylephrine has become firmly established as the vasopressor of choice, for both prophylaxis and treatment of spinal hypotension in obstetrics

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Vasopressor Infusion

- Currently, research continues to focus on optimizing the administration of phenylephrine
- Areas that have been studied include:
  - how phenylephrine could best be administered?
  - whether it should be used proactively (prophylactically) or reactively (only when spinal hypotension has occurred)?
  - whether continuous infusions are superior to bolus?
  - the appropriate dose to avoid side effects such as reactive hypertension and bradycardia (Hessen, 2015)
- Hessen (2014) – a meta-analysis looking at the use of phenylephrine for elective c - section
- Concluded that a continuous infusion (proactive treatment) started immediately after initiation of spinal can effectively reduce hypotension and nausea without inducing fetal acidosis compared with bolus doses given only in response to a fall in SBP (reactive treatment)

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Vasopressor Infusion Cont'd

- Although some anesthesia providers regard prophylactic phenylephrine infusion as too aggressive, the review by Heesen (2014) reassured that the risk of reactive hypertension has no difference between prophylactic and reactive regimens and the risk of bradycardia was also similar between groups.
- Study by Stewart et al. (2010) suggested that compared with higher doses, 25 – 50 µg/min give the lowest rate of both hypotension and hypertension.

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Norepinephrine – The Future Practice?

- Recently, norepinephrine has appeared as a potential alternative agent for treating spinal-induced hypotension in obstetric (O'Sullivan & Cockerham, 2016)
- The reason is the mixed α and β agonist activity of norepinephrine makes it a preferable drug for maintaining BP with less bradycardia, less negative effective on CO and no difference in fetal outcome compared with phenylephrine
- There is limited information available in the literature and few reports of its use in obstetrics.

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Norepinephrine – The Future Practice?

- Ngan Kee (2015) – double-blinded, 104 healthy patients having elective c - section were randomized to have SBP maintained with a computer-controlled infusion of norepinephrine 5 µg/ml or phenylephrine 100 µg/ml
- The primary outcome compared was CO, BP, HR and neonatal outcome
- The authors found that an infusion of norepinephrine maintained BP as effectively as phenylephrine, but with less bradycardia and less decrease in CO
- Also, no significant differences in neonatal outcomes

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Recommendations

- 5- HT3 Antagonist
  - Prophylactic 5-HT3 antagonist has an excellent effect on prevention of hypotension in healthy parturient
  - Most of the studies result support to give ondansetron 4mg **5 minutes before spinal**

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Recommendations

- Use of Vasopressor
  - Several studies have shown good results with a phenylephrine infusion for treatment of hypotension. But additional studies are needed (Cooper, 2012; Heesen et al., 2015; Ngan Kee et al., 2008; Khaw, 2006)
  - A good starting point is to start at 50 mcg/min straight after spinal injection and then titrate to response, with bolus if needed
- Future Research
  - More RCT should be conducted to determine the safety, optimal infusion rate and dosing strategy of norepinephrine in obstetric

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Conclusion

- Based on the clinical presentation of this case study and review of the latest evidence, a combination of pharmacological and non-pharmacological methods is beneficial in minimizing spinal - induced hypotension in elective cesarean delivery
- No single technique has been confirmed to be completely effective

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Thank You
Are There Any Questions?

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